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EXAMINER	
ISSAC, ROY P	
ART UNIT	**PAPER NUMBER**
1623	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,660	HARTH ET AL.	
	Examiner	Art Unit	
	Roy P. Issac	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,7 and 10-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,7 and 10-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/11/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The instant application is a 371 of PCT/US03/36705 which claims benefit of provisional applications 60/426,502 filed 11/15/2002, and 60/430,407 filed 12/02/2002.

This Office Action is in response to Applicant's amendment/ remarks/ response filed 02/05/2007, wherein claims 1, 5, 7, 10 and 14 were amended, claims 3, 4, 6, 8 and 9 were cancelled, and new claims 15-16 were newly submitted. Claims 1, 2, 5, 7, and 10-16 are currently pending and are examined on the merits herein.

Rejections Withdrawn

As indicated above, applicant's arguments/response filed 02/05/2007 cancelled claims 3, 4, 6, 8 and 9. All rejections and objections made with respect to the cancelled claims, 3, 4, 6, 8 and 9, in the previous office action are withdrawn.

The claim objections to claim 10 and 11-13 with respect to the use of the abbreviation α-Me-MSO is withdrawn since the abbreviation is replaced by the full chemical name in claim 10.

The Double patenting rejection under 35 U.S.C 101 with respect to claims 1-14 over co-pending application 10/715,679 is withdrawn, since applicants filed an express abandonment of the '679 application.

The rejection under 35 USC 112 first paragraph, with respect to claims 5-6 and 11-13 in regards to the lack of enablement for all gamma-substituted alpha amino-alpha-alkyl-butyrates is withdrawn, since applicants deleted the phrase "gamma substituted alpha amino alpha alkyl butyrates comprising" from claim 5.

The rejection under 35 USC 112 second paragraph, with respect to claims 1-13 in regards to the phrase "wherein said anti-mycobacerial composition effectively inhibits MbGS but does not substantially inhibit mammalian glutamine synthetase (MGS) in vivo" is withdrawn, since applicants deleted said phrase from claims 1, 5 and 10.

The rejection under 35 USC 102(b) of claims 1-2 over Lejczak is withdrawn since applicants amendments adding the recitation, "wherein if R2 is phosphonate, R1 is not methyl; if R2 is phosphonate, R1 is not methyl and if R2 is methyl sulfoximine, R1 is not methyl or ethyl" will overcome the anticipation rejection.

The following are new grounds of rejection necessitated by applicant's amendments:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 1, from which claim 2 depends is directed to a composition comprising a compound of formula I. Applicant's amendment with respect to claims herein has been fully considered, but is deemed to insert new matter into the claims since the specification as originally filed does not provide support for applicants' claim a composition comprising a compound of Formula I, "wherein if R2 is phosphonate, R1 is not methyl; if R2 is phosphonate, R1 is not methyl and if R2 is methyl sulfoximine, R1 is not methyl or ethyl." There are no working examples of any compounds that fall into the sub-genus description as it is now amended. The working examples 1-8 (pages 13-22) exemplify compounds methionine sulfoximine, and methyl or ethyl or buthionine substituted sulfoximines. As amended, all of these compounds are excluded from the generic formula I. There are no working examples of any compound that fall into the generic formula I as amended described in the specification as filed.

The description as originally filed does not provide support for the sub-genus as instantly claimed. The court held that "subgenus range was not supported by generic disclosure and specific example within the subgenus range"; See e.g. *In re Lukach,* 442 F.2d 967, 169 USPQ 795 (CCPA 1971); the court also held that "a subgenus is not necessarily described by a genus

encompassing it and a species upon which it reads" (see *In re Smith*, 458 F.2d 1389,1395, 173 USPQ 679, 683 (CCPA 1972). See also MPEP 2163.

Consequently, there is nothing within the instant specification which would lead the artisan in the field to believe that Applicant was in possession of the invention as it is now claimed. See *Vas-Cath Inc. v. Mahurkar*, 19 USPQ 2d 1111, CAFC 1991, see also *In re Winkhaus*, 188 USPQ 129, CCPA 1975.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Clifton et. al. (WO 95/15940; PTO-892).

Clifton et. al. discloses 2-amino-2-ethyl-4-phosphono-butanoic acid. (Compound 14, Page 25-26, Table 1). Clifton further discloses the use of compounds disclosed as pharmaceutical compositions comprising diluents and carriers. (Page 34 lines 21-24). The recitation "anti-mycobacterial composition" is considered the intended use of the claimed composition. Note that it is well settled that "intended use" of a composition or product, e.g., "anti-mycobacterial

composition", will not further limit claims drawn to a composition or product, so long as the prior art discloses the same composition comprising the same ingredients as the instantly claimed. See, e.g., *Ex parte Masham*, 2 USPQ2d 1647 (1987) and *In re Hack* 114, USPQ 161.

The following are new or modified rejections necessitated by Applicant's amendment filed 2/5/2007, wherein the limitations in pending claims 1-20 as amended now have been changed since claims 1, 5, 7, 10 and 14 were amended, claims 3, 4, 6, 8 and 9 were cancelled, and new claims 15-16 were newly submitted. The limitations in the amended claims have been changed and the breadth and scope of those claims have been changed. Therefore, rejections from the previous Office Action, filed 08/04/2006, have been modified and are listed below.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ

619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2, 5, 7 and 10-16 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 of U.S. Patent No. 6,013,660 in view of Griffith OW et. al (Of Record).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the '660 patent is drawn to a method of for treating mammalian disease conditions associated with infection of pathogenic mycobacterium comprising the steps of administering L-methionine-S-sulfoxmine (MS) to a mammal in a dose sufficient to significantly inhibit the growth or survival of the pathogenic mycobacterium without harming said mammal. The '660 patent further claims the use of said compound for the treatment of several mycobacterium bacteria including, M.tuberculosis, and M.avium. The '660 patent further attributes the activity of MS and its analogs to their ability to inhibit the activity of the extracellular enzyme glutamine synthetase (GS) an extracellular protein which is essential for the growth of M. tuberculosis and other closely related pathogenic intracellular mycobacteria. Inhibition of the activity of M. tuberculosis glutamine synthetase, specifically that enzyme which is released

extracellularly was found to inhibit the growth of M. tuberculosis cells resulting in the inhibition of bacterial growth. (Column 5, lines 50-61).

The claims of the instant application is drawn to compositions including alpha-alkylated methionine sulfoximines and methods of treating pathogenic mycobacterial infections using said compounds.

The '660 patent does not expressly disclose alpha alkylated L-methionine-S-sulfoximine or a racemic mixture of the same or other alpha alkylated butyrates for the treatment of pathogenic mycobacterium infection.

Griffith et. al. discloses the use of alpha-alkylated analogs of methionine sulfoximine, in particular alpha-ethyl-methionine sulfoximine for the selective inhibition of glutamine synthetase. (Page 2333, Abstract). Methionine sulfoximine is a known convulsant. (Page 2333, Column 1, Paragraph 2, lines 1-5). Griffith et. al. discloses that while methionine sulfoximine induces convulsions at a dosage of 1mmol/kg, alkylated methionine sulfoximines, in particular alpha-ethyl-methionine sulfoximines only produced convulsions at a much higher dosage. (Page 2335, Column 2, Paragraph 4, and Page 2336, Column 2, Paragraph 1). One of ordinary skill in the art would have reasonably expected that the instant compound, would have same or substantially similar beneficial therapeutic effects and usefulness in methods for treating, palliating or inhibiting mycobacterial infections in a mammal, based on the reasonable expectation that structurally similar species usually have similar properties. Herein, the branched and straight chain C1-C8 alkyl at R1 is considered structurally similar to the prior art compounds with methyl and ethyl groups at the R1 position. As noted in

MPEP 2144, "If such a species or subgenus is structurally similar to that claimed, its disclosure may motivate one of ordinary skill in the art to choose the claimed species or subgenus from the genus, based on the reasonable expectation that structurally similar species usually have similar properties. See, e.g., Dillon, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. See also Deuel, 51 F.3d at 1558, 34 USPQ2d at 1214. The utility of such properties will normally provide some motivation to make the claimed species or subgenus. Id. Dillon, 919 F.2d at 697, 16 USPQ2d at 1904-05 (and cases cited therein). If the claimed invention and the structurally similar prior art species share any useful property, that will generally be sufficient to motivate an artisan of ordinary skill to make the claimed species, In fact, similar properties may normally be presumed when compounds are very close in structure. Dillon, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. See also In re Grabiak, 769 F.2d 729, 731, 226 USPQ 870, 871 (Fed. Cir. 1985) ("When chemical compounds have very close' structural similarities and similar utilities, without more a prima facie case may be made."). Thus, evidence of similar properties or evidence of any useful properties disclosed in the prior art that would be expected to be shared by the claimed invention weighs in favor of a conclusion that the claimed invention would have been obvious. Dillon, 919 F.2d at 697-98, 16 USPQ2d at 1905; In re Wilder, 563 F.2d 457, 461, 195 USPQ 426, 430 (CCPA 1977); In re Linter, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972). Furthermore, a substantial number of the compounds encompassed by the generic formula I is considered homologs of the L-methionine-S-sulfoximine claimed in the '660 patent and the alkyl analogs of

methionine sulfoximine disclosed in Griffith et. al. The members of a homologous series must possess unexpected properties not possessed by the homologous compounds disclosed in the prior art. *In re Hass* 141 F.2d 127, 60 USPQ 548 (CCPA 1944). Adjacent homologs are considered to obvious absent unexpected results. *In re Henze* 85 USPQ 261, 263 (CCPA 1950).

One of ordinary skill in the art at the time the invention was made would have been motivated to employ alpha-alkylated methionine sulfoximines to treat mycobacterial infections because alpha-alkylated methionine sulfoximines were well known for their selective inhibition of glutamine synthetase and the '660 patent shows that the inhibition of glutamine synthetase by methionine sulfoximine leads to the inhibition of mycobacterial growth. Furthermore, aklylated methionine sulfoximines are advantageous because of their reduced tendency to induce convulsions.

Response to Arguments

Applicant's arguments filed 2/05/2007 with respect to this obviousness type double patenting rejection of record have been fully considered but they are not persuasive to render the claimed invention patentable as further discussed below.

Applicants argue that the amended claims cover compositions comprising a mycobacterial glutamine synthetase inhibitior of a genus that do not include L-methionine-S-Sulfoximine. Applicants further submit that claims 1 and 2 of the '660 patent are method of use claims while claims 1 and 2 of the instant

application are composition claims. As indicated above, the compounds claimed herein are considered to have strong structural similarity to both L-methionine-S-Sulfoximine and alkyl analogs of methionine sulfoximine. L-methionine-S-sulfoximine and alkyl analogs are compounds well known in the prior art as they are disclosed in the '660 patent and Griffith et. al. Applicants argument that claims in the'660 patent were directed to method of use claims while claims in the instant application are directed to composition claims was found unpersuasive since one of ordinary skill in the art would have found it obvious to make and use compounds of similar structure as those used in the methods of use claimed in the '660 patent. In regards to claims 5,7 and 10-16, applicants argue that mammalian glutamine synthase (GS) is a different protein with different structure than mycobacterial GS, and that Griffith 1978 discloses studies involving mammalian GS. This argument was found unpersuasive since claims in the '660 patent were drawn to a method of for treating mammalian disease conditions associated with infection of pathogenic mycobacterium comprising the steps of administering L-methionine-S-sulfoxmine (MS) to a mammal in a dose sufficient to significantly inhibit the growth or survival of the pathogenic mycobacterium without harming said mammal. The selective inhibition of mycorbacterium by L-methionine-S-sulfoximine is claimed in the '660 patent and the instant claims are directed to the selective inhibition of mycobacterial infection in mammal comprising compounds with strong structural similarity to L-methionine-S-sulfoximine. As such, the non statutory double patenting rejection is still deemed proper and is adhered to.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 5, 7 10-13, and 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harth et.al. (J.Exp. Med. 189(9), 1425-1435, 1999; Of Record), in view of Griffith et.al. (Methods in Enzymology, 143, 286-291; Of Record).

Harth et. al. teaches that pathogenic Mycobacteria secrets large number of proteins in to extracellular milleu. One of the abundantly released proteins is the enzyme glutamine synthetase. However, nonpathogenic mycobacterial microorganisms do not release glutamine synthetase into the extracellular milleu. (Page 1425, Column 2, last paragraph and Page 1426, Column 1, first paragraph). Harth et. al. further teaches that the inhibition of enzyme glutamine synthetase blocks bacterial multiplication. (Page 1426, Column 1. Paragraph 3). Harth et. al. teaches that inhibition of extracellular glutamine synthetase blocks bacterial multiplication both in broth medium and in human mononuclear phagocytes and that growth inhibition is correlated with a marked reduction in the amount of virulence-associated cell wall component poly-L-glutamate/glutamine.

(Page 1426, Column 1. Paragraph 3). Harth et. al. notes that; "Specifically, our study demonstrates that treatment of *M. tuberculosis* with a drug that inactivates extracellular glutamine synthetase inhibits mycobacterial growth. Hence, drugs functionally analogous to L-methionine-S-sulfoximine, but perhaps with even greater specificity for *M. tuberculosis* enzyme relative to the mammalian enzyme have great potential as antibiotics against this pathogen." (Page 1434, Colunn 1, Pargraph 5, line 13 to Column 2, paragraph 1, lines 1-6). Harth et. al. further compared the sensitivity of glutamine synthetase inhibitors on purified *M. tuberculosis* glutamine synthetase to mammalian glutamine synthetase. (Page 1427, Column 1, Paragraph 2, lines 10-15). Harth et. al. further discloses the use of conventional antibiotics in combination with L-Methionine-S-Sulfoximine, in particular isoniazid. Harth et. al. notes that, "The most pronounced effect on bacterial growth was observed for isoniazid and rifampin at one-tenth their minimal inhibitory concentrations in combination with 0.2μM L-methionine-S-sulfoximine." The authors further notes that, "This result is consistent with the hypothesis that the inhibitory effect of L-methionine-S-sulfoximine on the extracellular glutamine synthase effects the integrity of the M-tuberculosis cell wall so as to allow antibiotics greater access to the bacterial cytoplasm." (Page 1433, Column 2, Paragraph 2, lines 1-23). Harth et. al. further teaches that, of the possible four racemic forms of the inhibitor (D, or L)-methionine-(S or R)-sulfoxamine, only L-methionine-S-sulfoximine is active against glutamine synthetase. (Page 1429, Column 1, Paragraph 2, lines 7-11). The disclosed

concentratons of 0.2, 20 and 200μM inhibits mycobacterial growth and is considered an "anti-mycobacterial effective amount".

Harth et. al. does not expressly disclose the use of the particular α-alkylated compounds of formula I with methyl or ethyl substitution at the R-1 position for inhibiting, treating or palliating mycobacterial infections; in particular Harth et. al. does not disclose the use of alpha-methyl-(D or L)-methionine-(S or R)- sulfoxamine or alpha-methyl-L-methionine-S-sulfoxamine or alpha-ethyl-(D or L)-methionine-(S or R) -sulfoxamine or alpha-ethyl-L –methionine-S-sulfoxamine as anti-mycobacterial agents.

Griffith OW teaches that α-ethylmethionine sulfoximine, one of the mycobacterial inhibitors of the present application as a selective inhibitor of glutamine synthetase. Griffith OW notes that, "Selective inhibition of either glutamine synthetase or γ-glutamylcysteine synthetase is possible in vitro or in vivo using analogs of methionine sulfoximine. Thus, α-ethylmethionine sulfoximine inhibits only glutamine synthetase whereas prothionine sulfoximine inhibits only glutamine synthetase whereas porthionine sulfoximine, butathionine sulfoximine and higher S-alkyl analogs of methionine sulfoximine are specific inhibitors of γ-glutamylcysteine synthetase." (Page 287, Paragraph 1, lines 9-17).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use α-ethylmethionine sulfoximine as an inhibitor of mycobacterial glutamine synthetetase because, Griffith teaches that α-ethylmethionine sulfoximine is a selective inhibitor of glutamine synthetase and

Harth et. al. teaches that the growth of pathogenic mycobacteria can be inhibited by the inhibition of glutamine synthetase, in particular analogues of methionine sulfoximine.

One having ordinary skill in the art would have been motivated employ particular alpha-alkylated compounds herein, because, Harth et. al. suggests the use of analogues of methionine sulfoximine, and α-ethyl-methionine sulfoximine, the compound instantly claimed, is a well known analogue of methionine sulfoximine, known for its activity against glutamine synthetase. Furthermore, aklylated methionine sulfoximines are advantageous because of their reduced tendency to induce convulsions.

As noted in MPEP 2144, "If such a species or subgenus is structurally similar to that claimed, its disclosure may motivate one of ordinary skill in the art to choose the claimed species or subgenus from the genus, based on the reasonable expectation that structurally similar species usually have similar properties. See, e.g., Dillon, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. See also Deuel, 51 F.3d at 1558, 34 USPQ2d at 1214. The utility of such properties will normally provide some motivation to make the claimed species or subgenus. Id. Dillon, 919 F.2d at 697, 16 USPQ2d at 1904-05 (and cases cited therein). If the claimed invention and the structurally similar prior art species share any useful property, that will generally be sufficient to motivate an artisan of ordinary skill to make the claimed species, In fact, similar properties may normally be presumed when compounds are very close in structure. Dillon, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. See also In re Grabiak, 769 F.2d

729, 731, 226 USPQ 870, 871 (Fed. Cir. 1985) ("When chemical compounds have very close' structural similarities and similar utilities, without more a prima facie case may be made."). Thus, evidence of similar properties or evidence of any useful properties disclosed in the prior art that would be expected to be shared by the claimed invention weighs in favor of a conclusion that the claimed invention would have been obvious. Dillon, 919 F.2d at 697-98, 16 USPQ2d at 1905; In re Wilder, 563 F.2d 457, 461, 195 USPQ 426, 430 (CCPA 1977); In re Linter, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972).

As such, one of ordinary skill in the art would have had reasonably expected that alpha-alkyl-methionine-sulfoximine would also have anti-mycobacterial properties.

Thus, the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Response to Arguments

Applicant's arguments filed 2/05/2007 with respect to this rejection under 103(a) of record have been fully considered but they are not persuasive to render the claimed invention patentable as further discussed below.

Applicants argue that the prior art references cited by the examiner must provide motivation suggestion or teaching of the desirability of making he specific combination that was made by the application. As noted in the previous office action, if the claimed invention and the structurally similar prior art species share any useful property, that will generally be sufficient to motivate an artisan of

ordinary skill to make the claimed species, In fact, similar properties may normally be presumed when compounds are very close in structure. Furthermore, aklylated methionine sulfoximines, well known compounds in the prior art, are advantageous because of their reduced tendency to induce convulsions as disclosed by Griffith et. al. The applicants further argue that the prior art references cited by the PTO must suggest to one of ordinary skill in the art that the invention would have reasonable expectation of success. However, obviousness does not require absolute predictability, at least some degree of predictability is required. Herein structurally similar compounds were well known for their activity against mycobacterial infection and the alpha alkylated compounds were well known in the prior art, also known to have activity against mammalian glutamine synthetase. As such, one of ordinary skill in the art would have had reasonably expected that alpha-alkyl-methionine-sulfoximine would also have anti-mycobacterial properties.

Applicants further argue that Griffith et. al. at the time of the invention it was not known if the established inhibitors of mammalian GS would also inhibit mycobacterial GS. However, the rejection herein are based on structural similarity of established anti-mycobacterial agents. At the time of the invention, it was well known that L-methionine-S-sulfoximine was a potent anti-mycobacterial agent, and that compounds with similar structure exhibited activity against mammalian GS. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See

In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, Harth et. al. disclosed L-methionine-S-sulfoximine as an anti-mycobacterial agent and Griffith et. al.disclosed structurally similar alpha-alkyl-methionine-sulfoximine compounds with activity against mammalian GS. As such, the claimed invention herein is prima facie obvious over the combined teachings of the prior art. For the above reasons claims 1-2, 5, 7 10-13, and 15-16 are considered properly rejected under 35 USC 103(a) and is adhered to.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson ME. (Chemico-Biological Interactions, 111-112, 1998, 1-14; Of Record), in view of Harth et. al. (Of Record).

Anderson ME teaches that methionine sulfoximine is shown to inhibit both glutamine synthetase and γ-glutamylcysteine synthetase and it leads to convusions. (Page 5 last paragraph to page 6, lines 1-10). The γ-glutamylcysteine synthetase enzyme is involved in the synthesis of glutathione. (Abstract, and Page 2, Figure 2). Administration of methionine sulfoximine to rodents leads to convulsions. (Page 6, lines 3-7). Anderson ME recommends the use of ascorbate to prevent oxidative damage due to glutathione deficiency. (Page 6, paragraph 2).

Anderson et. al. does not expressly disclose the use of chirally pure L-methionine-(S or R)-sulfoximine enantiomer.

As discussed above, Harth et. al. discloses that of the possible four racemic forms of the inhibitor (D or L)-methionine-(S or R)-sulfoxamine, only L-methionine-S-sulfoximine is active against glutamine synthetase. (Page 1429, Column 1, Paragraph 2, lines 7-11).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to co-administer L-methionine-(S or R)-sulfoximine with ascorbic acid because ascorbic acid is well known to reduce convulsions associated with methionine sulfoximine and the L-methionine-S-sulfoximine enantiomer is known to be the active the agent against glutatmine synthetase.

One of ordinary skill in the art would have been motivated to co-administer ascorbic acid with L-methionine-(S or R)-sulfoximine because the combination is expected to produce beneficial therapeutic effects.

Response to Arguments

Applicant's arguments filed 2/05/2007 of this rejection under 103(a) of record have been fully considered but they are not persuasive to render the claimed invention patentable as further discussed below.

Applicants argue that there is no expectation of success nor motivation of suggestion to combine the teachings of Harth et. al. with the teachings of Anderson to achieve the claimed invention. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some

teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one of ordinary skill in the art would have been motivated to co-administer ascorbic acid because ascorbic acid is well knows to reduce convulsions and the administration of L-methionine-S-sulfoximine is known to cause convulsions in mammals, as pointed out in the previous office action. For the above reasons claim 14 is considered properly rejected under 35 USC 103(a) and is adhered to.

No claim is allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will

the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Roy P. Issac whose telephone number is 571-272-2674. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

4/16/07

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